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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,715	08/01/2001	Brad St. Croix	001107.00134	2480
22907	7590	03/13/2006	EXAMINER .	
BANNER & WITCOFF 1001 G STREET N W SUITE 1100 WASHINGTON, DC 20001			YAEN, CHRISTOPHER H	
			ART UNIT	PAPER NUMBER
			1643	

DATE MAILED: 03/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/918,715

**Applicant(s)**

ST. CROIX ET AL.

**Examiner**

Christopher H. Yaen

**Art Unit**

1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 22 August 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-10 and 18-37 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-10 and 18-37 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)             | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)          |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input checked="" type="checkbox"/> Other: <u>Exhibit 1</u> .            |

**DETAILED ACTION**

**Re: St. Croix et al**

1. The amendment filed 8/22/2005 is acknowledged and entered into the record. C
2. Claims 11-17 are canceled without prejudice or disclaimer, no claims added or amended with the filing of the paper of 8/22/2005.
3. Claims 1-10 and 18-37 are pending and examined on the merits.
4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Rejections Withdrawn - 35 USC § 101***

5. The rejection of claims 1-10 and 18-37 under 35 USC § 101 as lacking a specific and substantial well established utility is withdrawn in view of the persuasive arguments and declaration presented in the paper filed 8/22/2005. Specifically, applicant's arguments that the claimed antibody is specific for a protein that is expressed in tumor endothelium and provided a declaration by Dr. Kinzler which teaches the detection of tumor derived endothelial with an antibody that is specific for the extracellular domain. The rejection under 35 U.S.C. § 112, 1<sup>st</sup> paragraph as lacking a specific and substantial well established utility is also withdrawn in view of the persuasive arguments submitted in the paper filed 8/22/2005.

***Claim Rejections Withdrawn - 35 U.S.C. § 112, 1<sup>st</sup> paragraph***

6. The rejection of claims 26-30 under 35 USC § 112, 1<sup>st</sup> paragraph for new matter is withdrawn in view of the persuasive arguments set forth by the applicant in the paper filed 8/22/2005.

**NEW REJECTIONS**

***Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph***

7. Claims 1-10 and 18-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

**The nature of the invention**

The claims are drawn to a molecule comprising an antibody variable region which specifically binds to an extracellular domain (amino acids 19-426) of TEM 17 of SEQ ID No: 230. the claims are also drawn to the molecule further comprising a moiety. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

### **The breadth of the claims**

The claims as currently interpreted read on a single variable region on an antibody (i.e. a single  $V_H$  or  $V_L$  region).

### **The unpredictability of the art and the state of the prior art**

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an IL-1 $\beta$  antibody in

unspecified order and fused to any human or nonhuman framework sequence, have the required binding function. The specification provides no direction or guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional humanized antibody can be obtained by replacing the CDR regions of an acceptor antibody with the CDRs of a donor antibody. As evidenced by Adair et al. (PCT GB90/02017) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (p. 4). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed. It is suggested that the specific portion of the human constant region, which the variable region is covalently linked to, be explicitly recited within the claim or this language be removed completely in order to obviate this rejection. Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention

### **Working examples**

The specification of the instant application does not provided any working examples with regard to a "molecule" comprising a single variable region as claimed.

### **Guidance in the specification**

The guidance in the specification as filed teaches that antibodies can be labeled or conjugated to moieties, (see page 43, paragraph 103 for example). However, little guidance has been provided for molecules comprising a single variable region as claimed. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed. It is suggested that the claims be amended to recite an isolated antibody or antigen binding fragments, such that it would include the full complement of heavy and light chain CDR regions.

### **Level of skill in the art**

The level of skill in the art is deemed to be high.

### **Conclusion**

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

***Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph***

8. Claims 33-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION. Claims 33-37 recite a molecule that binds specifically to an amino acids residues 18-427 of TEM 17. The specification on page 32 teaches that the extracellular domain of TEM 17 is represented by amino acids 1-426, wherein the signal peptide (i.e. amino acids 1-18) is cleaved from the mature protein leaving an extracellular domain comprising amino acids 19-426. The specification does not support isolated "molecules" that specifically bind amino acid residues 18-427 as claimed, because this epitope or domain has not been previously contemplated or disclosed. It is noted that applicant may overcome this rejection by reciting an epitope or domain of 19-426 as defined on page 32.

***Claim Rejections - 35 USC § 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

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only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-10 and 18-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Drmanac *et al* (US Patent 6,667,391) as evidenced by Harlow *et al* (Harlow *et al* , Antibodies, A Laboratory Manual, Chapter 5, 1988). Drmanac *et al* antibodies that bind to a sequence of SEQ ID No: 23 which shares 42.7% overall sequence identity to SEQ ID No: 230 of the instant application. SEQ ID No: 23 as disclosed by Drmanac *et al* shares several regions of overlap with the extracellular domain of TEM 17, such as within amino acids 280-344 as claimed (see attached sequence alignment - exhibit 1). It is well known and established in the art that antibodies will cross react and bind to epitopes as small as 6 residues in length (Harlow *et al* , Antibodies, A Laboratory Manual, Chapter 5, page 76, 1988) and still retain the binding ability to the original protein (Harlow *et al*. page 76). Therefore, the antibodies (i.e. polyclonal antibodies) as disclosed by Drmanac would bind to regions within the instantly claimed TEM 17 protein of SEQ ID No: 230. Drmanac *et al* also teach various types of antibodies such as polyclonal antibodies, monoclonal antibodies, antibody fragments, human antibodies, and antibodies conjugated to diagnostic agents and therapeutic agents (see col. 67-69). For the purposes of this rejection, antibodies labeled with I<sup>125</sup>, as disclosed by Drmanac *et al*, are interpreted as cytotoxic, therapeutic, and anti-tumor moieties as claimed. In addition, the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the population of antibodies as disclosed by Drmanac *et al* would not comprise an antibody that cross reacts with and binds to TEM17 protein of SEQ ID No: 230, and therefore the antibody of the prior art cannot be

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established as being patentable distinct from that instantly claimed. In the absence of evidence to the contrary, the burden is on the applicant to prove that the antibody or "molecule" claimed is different from that taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H. Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen, Examiner  
Art Unit 1643  
March 6, 2006

  
CHRISTOPHER YAEN  
PATENT EXAMINER

Exhibit 1

```
Db 65 WKRVV--DPEKAVUTNRASMGQASBESKGFPTDLIDGQDNNTQBEPTDNTYIISRTYG 122
Qy 82 PSEPHSELWVDVAENNSQYKHTILNSTRQASRVLSPEPPYGHPLQITLTCGF 141
Db 123 PADASDLWNIDOMEKDKYKHGILNSTRQARVLSDFPPYGHPLNBRVATATGCF 182
Qy 142 IPMDVIRHMTLTAQYVAPLMANRPGVSDNS--VYFPNGVTVVQMDHVLQGMEDKGS 201
Db 183 IYTBVVRHMLTATQYVAPLMANRPGVSRNSTVARYFPNGTALVQMDHVLQONTNIGS 242
Qy 202 FTFOALHHDGRIVAYKGIPEISQHPVYTGSDAFMILNPEPDVPSRRRIIF 261
Db 243 FTFOALHHDGRITFGYKELIVLTQSSNHPKVGSDAFVVRHIOQLPNRRRTTY 302
Qy 262 EYHRIELDPSKYVPSAVEFTPLPTCLOHRSQDACSMDLTJFNCSCWCHVLCRCSGPDY 321
Db 303 EYHRIELDPSKYVPSAVEFTPLPTCLOHRSQDACSMDLTJFNCSCWCHVLCRCSGPDY 362
Qy 322 ROEMNDYGCAGABG--RMCEDFODEHDSAPDTSFPYDGLTTTS---SLFIDSL 375
Db 363 ROEMNDYGCAGABG--RMCEDFODEHDSAPDTSFPYDGLTTTS---SLFIDSL 422
Qy 376 TTEDDTKLNPYAGDGLQ--NNLSPTKGTVPVHAGTI 410
Db 423 TTEDDTKLNPYAGDGLQ--NNLSPTKGTVPVHAGTI 458
```

## RESULT 8

US-09-764-325A-23  
Sequence 23, Application US/09764325A

PATENT NO. 6667391  
GENERAL INFORMATION:

APPLICANT: Labat, Ivan  
APPLICANT: Dmanac, Radoje T.

APPLICANT: Tang, Y. T.  
APPLICANT: Chao, Cheng-Chi

APPLICANT: Mize, Nancy K.  
APPLICANT: Childs, John

TITLE OF INVENTION: Methods and Materials Relating to No. 6667391el Stem Cell  
FILE REFERENCE: 30266/37630A

CURRENT APPLICATION NUMBER: US/09/764,325A  
CURRENT FILING DATE: 2001-01-16

PRIOR APPLICATION NUMBER: 09/547,358  
PRIOR FILING DATE: 2000-04-11

PRIOR APPLICATION NUMBER: 09/545,714  
PRIOR FILING DATE: 2000-04-07

PRIOR APPLICATION NUMBER: 09/488,725  
PRIOR FILING DATE: 2000-01-21

NUMBER OF SEQ ID NOS: 25  
SOFTWARE: Patent In Ver. 2.1

SEQ ID NO 23

LENGTH: 392

TYPE: PRT

ORGANISM: Homo sapiens

US-09-764-325A-23

Query Match 42.7%; Score 948; DB 4; Length 392;  
Best Local Similarity 57.9%; Pred. No. 66-85;  
Matches 184; Conservative 51; Mismatches 77; Indels 6; Gaps 3;

Qy 99 RSOVKHTILNSTRQASRVLSPEPPYGHPLQITLTCGFIPMDVIRHMTLTAQYV 158  
Db 3 KDKVKHIGILNSTRQARVLSPEPPYGHPLQITLTCGFIPMDVIRHMTLTAQYV 62  
Qy 159 APLMANRPGVSDNSTVYFPNGTALVQMDHVLQGMEDKGSFTFOALHHDGRIVAY 218  
Db 63 APLMANRPGVSDNSTVYFPNGTALVQMDHVLQGMEDKGSFTFOALHHDGRIVAY 122  
Qy 219 KEIPMSVPEISSQHPVYTGSDAFMILNPEPDVPSRRRIIFEXHRIELDPSKYTMSA 278  
Db 123 KEIPMSVPEISSQHPVYTGSDAFMILNPEPDVPSRRRIIFEXHRIELDPSKYTMSA 182

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Qy 279 VERTPLPTCLOHRSQDACSMDLTJFNCSCWCHVLCRCSGPDYRQEMNDYGCAGABG 338
Db 183 VERTPLPTCLOHRSQDACSMDLTJFNCSCWCHVLCRCSGPDYRQEMNDYGCAGABG 242
Qy 339 CEDFODEHDSAPDTSFPYDGLTTTS---SLFIDSLTTEDDTKLNPYAGDGLQ 393
Db 243 CEDFODEHDSAPDTSFPYDGLTTTS---SLFIDSLTTEDDTKLNPYAGDGLQ 302
Qy 394 --NNLSPTKGTVPVHAGTI 410
Db 303 TDESAKKGGLTLAGLI 320
```

## RESULT 9

US-09-764-325A-25  
Sequence 25, Application US/09764325A

PATENT NO. 6667391  
GENERAL INFORMATION:

APPLICANT: Labat, Ivan  
APPLICANT: Dmanac, Radoje T.

APPLICANT: Tang, Y. T.  
APPLICANT: Chao, Cheng-Chi

APPLICANT: Mize, Nancy K.  
APPLICANT: Childs, John

TITLE OF INVENTION: Methods and Materials Relating to No. 6667391el Stem Cell  
FILE REFERENCE: 30266/37630A

CURRENT APPLICATION NUMBER: US/09/764,325A  
CURRENT FILING DATE: 2001-01-16

PRIOR APPLICATION NUMBER: 09/547,358  
PRIOR FILING DATE: 2000-04-11

PRIOR APPLICATION NUMBER: 09/545,714  
PRIOR FILING DATE: 2000-04-07

PRIOR APPLICATION NUMBER: 09/488,725  
PRIOR FILING DATE: 2000-01-21

NUMBER OF SEQ ID NOS: 25  
SOFTWARE: Patent In Ver. 2.1

SEQ ID NO 25

LENGTH: 392

TYPE: PRT

ORGANISM: Homo sapiens

US-09-764-325A-25

Query Match 42.7%; Score 948; DB 4; Length 392;  
Best Local Similarity 57.9%; Pred. No. 66-85;  
Matches 184; Conservative 51; Mismatches 77; Indels 6; Gaps 3;

Qy 99 RSOVKHTILNSTRQASRVLSPEPPYGHPLQITLTCGFIPMDVIRHMTLTAQYV 158  
Db 3 KDKVKHIGILNSTRQARVLSPEPPYGHPLQITLTCGFIPMDVIRHMTLTAQYV 62  
Qy 159 APLMANRPGVSDNSTVYFPNGTALVQMDHVLQGMEDKGSFTFOALHHDGRIVAY 218  
Db 63 APLMANRPGVSDNSTVYFPNGTALVQMDHVLQGMEDKGSFTFOALHHDGRIVAY 122  
Qy 219 KEIPMSVPEISSQHPVYTGSDAFMILNPEPDVPSRRRIIFEXHRIELDPSKYTMSA 278  
Db 123 KEIPMSVPEISSQHPVYTGSDAFMILNPEPDVPSRRRIIFEXHRIELDPSKYTMSA 182  
Qy 279 VERTPLPTCLOHRSQDACSMDLTJFNCSCWCHVLCRCSGPDYRQEMNDYGCAGABG 338  
Db 183 VERTPLPTCLOHRSQDACSMDLTJFNCSCWCHVLCRCSGPDYRQEMNDYGCAGABG 242  
Qy 339 CEDFODEHDSAPDTSFPYDGLTTTS---SLFIDSLTTEDDTKLNPYAGDGLQ 393  
Db 243 CEDFODEHDSAPDTSFPYDGLTTTS---SLFIDSLTTEDDTKLNPYAGDGLQ 302  
Qy 394 --NNLSPTKGTVPVHAGTI 410  
Db 303 TDESAKKGGLTLAGLI 320